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OPINION REVIEW

Emerging role of biosimilars in the clinical care of inflammatory bowel disease patients

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Abstract

The increasing incidence of inflammatory bowel disease (IBD) globally has redirected the healthcare system's focus towards safe and affordable pharmacological interventions. The inception of anti-tumor necrosis factor-α (TNF-α) had resulted in a trend shift from surgical interventions. However, as the patents of approved anti-TNF-α drugs expire, biological copies of the many approved products are in the pipeline. The most commonly used biosimilar for IBD has been infliximab, followed by Adalimumab biosimilars which have been approved in major countries across the world. Although biosimilars are approved on the basis of similarity of their reference product, the lack of real-world evidence of its safety in ulcerative colitis and Crohn's disease patients has contributed to physicians' hesitancy. However, biosimilars are expected to reduce treatment costs and provide economic benefits.

Key Words: Inflammatory bowel disease; Biosimilars; Anti-tumor necrosis factor; Infliximab; Adalimumab; Ulcerative colitis; Chrons disease

Core Tip: There is limited evidence on the safety and use of biosimilars other than Infliximab. This review explores the role of biosimilars in an era of anti-tumor necrosis factor-α drug as a treatment option for inflammatory bowel disease. The approval of biosimilars by the Food and Drug Administration or European Medicines Agency based on their similarity and functionality to the reference product has raised concerns regarding its efficacy. Many remain hesitant in recommending biosimilars as a viable treatment option, despite its promise of reducing long-term costs. This originates from the lack of clinical trials of biosimilars. Although no serious adverse events have been reported with biosimilars, conclusions cannot be drawn without sufficient empirical evidence.

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INTRODUCTION

The idiopathic Inflammatory Bowel Disease (IBD) phenotypically presents as ulcerative colitis (UC) and as Crohn's disease (CD). Unlike UC, which exclusively affects the colon's mucosal layer, CD damages all layers of the gastrointestinal tract[1]. Clinical presentations that are common to both subtypes include diarrhea and abdominal pain. Rectal bleeding in UC patients and perianal bleeding in CD are caused by excessive chronic inflammation and a dysregulated immune system[2]. A compromised intestinal barrier allows infiltration of leukocytes, and the release of pro-inflammatory cytokines and interleukins (IL) from T-regulatory cells and Th17 cells which exaggerate inflammation. Contributing factors as IL-6, IL-17, interferon-gamma (IFN-γ), free oxidative radicals, and tumor necrosis factor-α (TNF-α); high serum levels and biopsy specimens of TNF-α are definitive markers of CD and colitis[3]. Increased exposure of leukocytes to the lumen antigens exasperates tissue injury[3]. Although the etiology of IBD remains unclear, normal gut flora is increasingly suspected to be affected by environmental and genetic factors, triggering an immune response[4].

The incurable IBD, often regarded as the 'disease of the west,' shows increase incidence and prevalence in developing countries of Asia, Africa, and Europe[2], due to recent industrialization. A review reported a 67% increase in IBD-related deaths until 2017[2], advocating alternate treatment choices that improve quality of life.

Conventional treatment for IBD aims to reduce inflammatory mechanisms, maintain the patient in remissions, and relieve symptoms. Five-aminosalicylates and Sulfazialine are the first-line of treatments for patients suffering from UC. However, Sulfazialine is not well tolerated in allergic patients[5]. The routine use of corticosteroids with Azathioprine and Mesalamine aims to maintain remission rates in UC and CD patients. Long-term complications associated with steroid therapy include hyperglycemia, diabetes mellitus, and aseptic joint necrosis. Moderate to severe CD patients receiving steroid therapy often develop steroid resistance and steroid dependence, which increases the risk of sepsis[6]. The high rates of mortality and relapsed remission rates have become a major attraction for researchers worldwide.

Newer treatments focus on the anti-TNF-α antibody cA2 regime to reduce the major inflammatory stimulus. Of the five approved biologics, the commonly used for IBD are infliximab, adalimumab, and etanercept[7]. The anti-TNF-α antibody cA2 regime has expanded to include the anti-adhesion agents (natalizumab, vedolizumab) and antibodies that inhibit IL 12 and 23 (ustekinumab)[8]. IBD has emerged as a burden on the healthcare system; pharmacological interventions such as anti-TNF- α has emerged as the industry's prime focus compared to surgical procedures[9]. Consequently, the global pharmaceutical market has succeeded in producing therapeutic drugs despite the costs involved[10]. However, as patents for biologics expired, the production of complex drugs, named biosimilars, began in the early 2000s[11].

THE EMERGENCE OF BIOSIMILARS IN AN ERA OF ANTI-TNF-ALPHA

A biosimilar is a biological copy of a Food and Drug Administration (FDA)-approved originator drug that produces no clinical differences compared to the reference product (RP)[8]. Biosimilars such as monoclonal antibodies have a complex quaternary structure that is prone to post-translational modification, and as a result, it may slightly differ from the reference drug[12]. The European Medicines Agency (EMA) laid down a rigorous but accelerated approval pathway in 2005; the Biologics Price Competition and Innovation Act (BPCIA) in 2009 adopted a similar framework, followed by the FDA in 2012. Biosimilars have been designed to introduce competition in the global market while providing

cost-effective solutions to the health industry[10]. The regulatory process explains that expedited biosimilar product approval is possible because of extrapolation. This allows the biosimilar product to be approved for all indications of the originator product without being tested for it; as a result, saving cost for funding to carry out rigorous trials[13].

THE LANDSCAPE OF BIOSIMILARS FOR IBD IN CLINICAL SETTINGS

Given the safety and efficacy of anti-TNF-α monoclonal antibodies, the first biosimilar product for IBD to receive approval was an RP of infliximab; CELLTRION, Inc, Incheon in South Korea developed a biosimilar product CT-P13[14]. The EMA licensed CT-P13 for IBD use in 2013, while FDA did not approve infliximab-dyyb until 2016. Regulatory approval was given based on two randomized clinical trials (RCTs)[12,15] that analyzed similarities in pharmacodynamics and pharmacokinetics to the RP; phase 1 of clinical testing in active rheumatoid arthritis (RA) patients (PLANETRA)[12] and phase 3 in ankylosing spondylitis (AS) patients (PLANETAS)[15] led to CT-P13's approval. Simple extrapolation led to its approval for UC and CD in the United States, the United Kingdom, Europe, Korea, Australia, and Canada[14].

Infliximab biosimilar SB2 (Flixabi or Renflexis) followed a similar approval pathway from the EMA in 2016 and by the FDA in 2017, while PF-06438179 (Zessly) has only been licensed for use in Europe. India's health ministry approved biosimilar BOW015 (Infimab) as a treatment for IBD in 2014[16]; while NI-071[17] and STI-002[18] completed phase III trials in China and Japan, maintaining the safety and efficacy of the RP at the end of the 54-wk study period.

Another anti-TNF-α IgG1 monoclonal antibody, Adalimumab (ADA) originator, had the expiry of their patents in 2016 in the United States and 2018 in Europe[19,20]. Since then, biosimilars for ADA have been introduced in the clinical setting. The first ADA biosimilar to gain approval was ABP 501 (Amigen) by the FDA in 2016 and the EMA in 2017. The 52-wk clinical trial of ABP 501 in moderate-to-severe RA patients[21] and psoriasis patients[21] concluded that there were no significant differences between the biosimilar and the RP in the efficacy (PASI scores and ACR20 Levels). SB5 (Imraldi), a biosimilar product of ADA, was approved by the EMA in 2017 and exhibited similar pharmacokinetics and response rates (72%) at 24 wk of the trial[22].

Table 1 summarizes the list of biosimilars, originator products, and the country of approval. However, it is essential to note that most biosimilar products were only clinically tested in RA or AS patients. VOLTAIRE®-PK trial of BI 695501[23], a biosimilar product of the originator ADA serves as an example of clinical trials among healthy volunteers. EMA has approved three infliximab biosimilars (CT-P13, SB2, and PF-06438179/GP1111) and five adalimumab biosimilars (ABP501, SB5, FKB327, GP2017, and MSB11022) for all complications of the RP and, therefore, IBD subtypes. However, in the United States, only two infliximab biosimilars (CT-P13, SB2) and three adalimumab biosimilars (ABP501, SB5, GP2017) are FDA-licensed for use[24]. Nonetheless, a snapshot review from 2020 reports the increasing trend of biosimilar approvals in the United States, showing the United States government's interest to encourage cost-effectiveness[25].

Introducing competition in the market reportedly decreased the listed prices of originator products for IBD treatment in the European market[26]. With the biosimilar product's introduction to the market, the UK and France saw a decrease in the sales of the originator infliximab[27]. A stochastic-cost model of the Netherlands predicted a significant reduction in UC and CD patients' hospitalization charges and originator product prices over five years[24].

REAL-WORLD EVIDENCE AND THE STANCE OF HEALTHCARE PROFESSIONALS ON BIOSIMILARS FOR IBD

Despite the case-by-case consideration of each biosimilar before its approval, extrapolation has raised concerns about its safety amongst clinicians. A cohort described the acceptance rates of biosimilars among gastroenterologists; 80% of physicians prescribed the first-line originator treatment over biosimilars[26]. In another study that assessed physicians' willingness to switch from infliximab, 72.8% refrained from prescribing biosimilars. Of the 23.7% prescribed biosimilars and biologics, only 60% switched patients from originator treatment to biosimilars[28].

The European Crohn's Colitis Organisation (ECCO) and IBD societies had raised caution against biosimilar drugs approved for IBD[29]. A position paper by the Spanish Agency of Medicines and Medical Devices expressed disagreement with the EMA's approval of biosimilars[30]. Reluctance to prescribe biosimilars lies in its approval process, which does not require large clinical trials. Additionally, the lack of real-world evidence for each approved biosimilar product and the consequences of "switching" is unclear. In the European region, the physician determines if switching from one medicine to another is required based on the clinical effects' similarity. Contrary to the practices in Europe, interchangeability is carried out between biologics and biosimilars at the pharmacy

Table 1 Summary of originator biologic products of tumor necrosis factor-α inhibitors and biosimilars

Product	Biosimilar	Country/year	Status
Infliximab (Remicade, Janssen)	CT-P13 (Inflectra or Remsima, Celltrion Healthcare)	USA, EU, Japan	Approved
	SB2 (Flixabi or Renflexis)	EU, Korea, Australia, USA	Approved
	PF-06438179 or GP1111 (Zessly)	EU-2019	Approved
	BOW015 (Infimab)	India-2014, USA, Canada, Europe, Thailand	Approved; pending market approval
	CMAB008	China-2020	Under review/submitted
	Baimaibo	China-2019	Under review/submitted
	NI-071	Japan-2019	Ongoing-Phase III trial completed
	STI-002	China-2016	Ongoing-Phase III trial completed
Adalimumab (Humira, AbbVie)	ABP 501 (Amgen)	USA-2016, Europe-2017	Approved
	SB5 (Imraldi)	Europe-2017	Approved
	ZRC-3197 (Exemptia)	India-2014	Approved
	BI 695501	USA-2017	Approved
	GP2017	Europe-2017	Approved
	FKB327 (Huilo)	Europe-2019	Approved
	PF-06410293 (Amsparity/Abrilada)	Europe and USA-2020	Approved
	LBAL (Adalimumab BS MA)	Japan-2021	Approved
	CHS-1420	USA-2021	Ongoing-Phase III trial completed
	ONS-3010	Europe-2018	Ongoing-Phase III trial
	BOW050	Europe-2017	Under review
	MSB11022	Europe-2019	Under review
	M923	-	Discontinued
Golimumab	BOW100	-	Under review
	BAT2506	Europe and USA	Ongoing-Phase III trial
Certolizumab	PF688	USA	Under review
Pegol	Xcimzane	-	Ongoing

EU: European Union; USA: United States.

level in the United States, without a healthcare worker's expert opinion [31].

The NOR-SWITCH trial[32] and PROSIT-BIO[33] observational cohorts support the switch from Infliximab to CT-P131 in IBD patients; Massimi *et al*[34] in a prospective study of UC and CD patients from 2021, verified a safe switch from Infliximab to SB2 biosimilar product. A meta-analysis in 2017 analyzed 11 observational studies for the efficacy of CT-P131 in comparison with the Infliximab originator[33]; a recent network meta-analysis concluded that CT-P131's pharmacodynamics is an excellent treatment for remission maintenance. Thus, physicians are confident prescribing infliximab biosimilars, but not biosimilars of other approved anti-TNF-α treatments.

MARKET SALES OF BIOSIMILARS WORLDWIDE

A study from 2021 concluded that Europe dominated the biosimilars market share worldwide by 50%, forecasted to top the charts until 2030[35]. Despite the increasing incidence of chronic diseases, biosimilar sales staggered to achieve 9% of the projected $1 billion cost savings[36]. Due to a lack of definitive standards for approval, adequate profitability, and the risks involved in switching, the United States' biosimilars market growth remains stagnant[37].

FUTURE CHALLENGES AND RECOMMENDATIONS

The lack of empirical evidence and real-world data about the safety of biosimilars in different population groups diagnosed with IBD remains a concern. A study enrolled 42 patients with CD or UC and reported no changes in C-reactive protein, erythrocyte sedimentation rate, or albumin[38]. However, studies with larger sample sizes are required to draw a safe conclusion. Non-medical switching from biologics to biosimilars may ensue a treatment failure, namely the "nocebo effect". In this case, the differences could arise from the individuals' response to the unidentical molecules of the biosimilars. Additionally, 38% of the patients who were switched from originator therapy to biosimilars were unaware of the switch[39]; consultation, written or verbal consent, and patient-doctor communication can minimize the nocebo effect in such patients[40].

Double switch[41] from originator to biosimilars and from one biosimilar to another has recently emerged as a new concern for safety, efficacy, and cost-effectiveness. With patents expiring and multiple biosimilars under review, such queries are bound to emerge more frequently, requiring regulatory bodies' guidelines.

The practice of tendering regulates the cost and availability of pharmaceuticals at the hospital level across Europe. While awarding grants, tendering bodies account for biosimilars and biologics' cost, efficacy, and safety[42]. Tenders may focus on immediate cost reduction of biologics or decrease suppliers and market competition[43].

It is imperative to understand the prospect of IBD patients who experience a secondary loss of response to anti-TNF-α biologic. With only one study measuring the cross-reactivity of anti-infliximab antibodies to infliximab-dyyb in IBD patients, the treatment of such individuals becomes a challenge [13].

Though biosimilars are estimated to reduce costs, the extent of savings and insurance costs are unclear to the patients. Non-medical switching is concerning as insurance companies and government policies might favor adopting biosimilars entirely, even if not required. New data from upcoming studies is necessary to bridge the knowledge gap in healthcare professionals. Overcoming physicians' hesitancy to prescribe biosimilars is required to increase public health literacy while communicating the evidence-based risks in biologics or biosimilars[29].

CONCLUSION

The introduction of biosimilars is expected to reduce the economic burden on the healthcare system while allowing the repurposing of funds towards life-saving drugs and procedures. Based on the available literature, biosimilars are safe and efficacious alternatives to anti-TNF biologic drugs for patients with Inflammatory Bowel Disease. It is important that clinicians should be familiar with the biosimilars, its approval process, cost, safety profile, and the clinical efficacy to help provide the best cost-effective care for their patients. The varying trends in biosimilar research, approvals, and marketing sales point towards them becoming a standard treatment option, with regulatory bodies playing an essential role in deciding. Phase III and IV clinical trials of biosimilar products and real-world comparison of originator and biosimilar are required to improve biosimilar advocacy and education.

FOOTNOTES

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